Spatial-temporal targeting of lung-specific mesenchyme by a Tbx4 enhancer.

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Public Summary:

Scientific Abstract:

BACKGROUND: Reciprocal interactions between lung mesenchymal and epithelial cells play essential roles in lung organogenesis and homeostasis. Although the molecular markers and related animal models that target lung epithelial cells are relatively well studied, molecular markers of lung mesenchymal cells and the genetic tools to target and/or manipulate gene expression in a lung mesenchyme-specific manner are not available, which becomes a critical barrier to the study of lung mesenchymal biology and the related pulmonary diseases. RESULTS: We have identified a mouse Tbx4 gene enhancer that contains conserved DNA sequences across many vertebrate species with lung or lung-like gas exchange organ. We then generate a mouse line to express rtTA/LacZ under the control of the Tbx4 lung enhancer, and therefore a Tet-On inducible transgenic system to target lung mesenchymal cells at different developmental stages. By combining a Tbx4-rtTA driven Tet-On inducible Cre expression mouse line with a Cre reporter mouse line, the spatial-temporal patterns of Tbx4 lung enhancer targeted lung mesenchymal cells were defined. Pulmonary endothelial cells and vascular smooth muscle cells were targeted by the Tbx4-rtTA driver line prior to E11.5 and E15.5, respectively, while other subtypes of lung mesenchymal cells including airway smooth muscle cells, fibroblasts, pericytes could be targeted during the entire developmental stage. CONCLUSIONS: Developmental lung mesenchymal cells can be specifically marked by Tbx4 lung enhancer activity. With our newly created Tbx4 lung enhancer-driven Tet-On inducible system, lung mesenchymal cells can be specifically and differentially targeted in vivo for the first time by controlling the doxycycline induction time window. This novel system provides a unique tool to study lung mesenchymal cell lineages and gene functions in lung mesenchymal development, injury repair, and regeneration in mice.

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